REMARKS

Reconsideration of the rejections set forth in the Office action mailed June 3, 2003 is respectfully requested, for the reasons discussed below.

The applicants thank the Examiner for granting a telephonic interview regarding the above-referenced application on August 29, 2003. An Interview Summary is enclosed herewith. As noted below, certain amendments were proposed by the applicants, and the Examiner indicated that they would be favorably received.

I. Amendments

In independent claim 1, the preamble is amended to recite "separating a population of duplexes comprising different oligomeric analyte molecules", in accordance with the last step of the method recited in the claim.

Claim 1 is also amended to recite that the oligomeric analyte molecules are composed of linked subunits of which at least 90% are uncharged. Support is found in the specification at, for example, page 8, lines 16-17.

Claim 1 is also amended to recite that the specific probe molecule is a nucleic acid or fully charged nucleic acid analog. Support is found in the specification at, for example, page 12, line 23.

The above amendments were discussed in the telephone interview of August 29, 2003, and the Examiner indicated that they would be favorably received.

The follow additional amendments are made in view of the foregoing:

The second clause of claim 1 is amended (changing "the population of analyte molecules" to "the different analyte molecules") to reflect the amended language of the first clause.

Claim 18 is cancelled, and claim 19 is amended to depend from claim 1.

No new matter is added by any of the amendments.

II. The Invention

The applicant's invention, as embodied in independent claim 1, provides a method of separating a population of duplexes comprising different oligomeric analyte molecules which are substantially uncharged. Each analyte molecule is able to hybridize with a specific charged

probe molecule, which is a nucleic acid or a fully charged nucleic acid analog. The method comprises the steps of:

(a) applying the analyte molecules and the probe molecule to a charge-bearing separation medium, under conditions such that the probe forms stable duplexes with a plurality of or all of the analyte molecules,

thereby forming a mixture of species selected from probe-analyte duplexes, single stranded analyte, single stranded probe, and combinations thereof; and

(b) separating the duplexes from each other and from single stranded species within the medium.

It is the discovery of the applicants that the duplexes of the different (substantially uncharged) analyte molecules with the (charged) probe molecule can be separated in a charge-bearing separation medium. The charged-based separation is believed to arise from the differing amounts of unconstrained single stranded charged probe molecule in the different duplexes. See, for example, the discussion at page 9 of the specification, with reference to Figs. 3-4. This method permits separation of the substantially uncharged oligomers without the use of the extreme pH ranges described in the prior art.

III. Rejections under 35 U.S.C. §102(b) and 103(a) in view of Summerton *et al.*

Claims 1-5, 10, 15, and 18-27 were rejected under 35 U.S.C. §102(b) as being anticipated by Summerton *et al.*, U.S. Patent No. 5,034,506. Claim 6 was rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*

As an outcome of the interview conducted on August 29, 2003, the Examiner agreed that the above-noted amendments would overcome this reference.

To summarize the conclusions reached in the interview, the reference does not show or suggest step (a) of the claim, namely:

(a) applying to a charge-bearing separation medium a mixture of (i) different (substantially uncharged) analyte molecules and (ii) a (charged) probe molecule, under conditions such that the probe forms stable duplexes with a plurality of or all of the analyte molecules,

thereby forming a mixture of species selected from probe-analyte duplexes, single stranded

analyte, single stranded probe, and combinations thereof.

Nor would a skilled person be motivated to modify the reference teachings along the lines of the claim. For example, the reference describes separation of different uncharged oligomers on an ion exchange column (see e.g. column 12, line 42 to column 13, line 12), but there is no suggestion, nor would there be any reason, to include a charged nucleic acid probe molecule in such a procedure, or to attempt to separate duplexes on the column. Because the separation is carried out at high or low pH, to ionize the bases of the uncharged oligomers, as stated in the reference (see column 12, lines 42-48 of the patent), no duplexes could stably form under the conditions of separation.

The reference also describes a solution containing a single uncharged oligomer and a single DNA molecule ("its complementary DNA"; column 33, line 24). However, this solution is used for determining binding of the oligomer to its complementary DNA, where binding is measured spectrophotometrically (see e.g. column 34, lines 45-69). There is clearly no motivation provided to apply such a solution to a "separation medium", nor to include multiple, different uncharged oligomers.

In the interview of August 29th, the Examiner also referred to column 18, lines 24-30 of the '506 patent: "...morpholino-based polymers can be fixed to a solid support and used to isolate complementary nucleic acid sequences, for example, purification of a specific mRNA from a poly-A fraction...". However, the applicants pointed out that, in this process, the probe is substantially uncharged (the morpholino-based polymer) and the analytes are charged (a poly-A fraction of mRNA or other nucleic acid sequences).

In addition, this method does not comprise "(a) applying to a charge-bearing separation medium a mixture" of analytes and probe, since the probe is affixed to the solid support, and thus only the analytes are applied.

In view of the foregoing, and in accordance with the conclusions reached in the interview of August 29, the applicants respectfully request the Examiner to withdraw the rejections in view of this reference under 35 U.S.C. §102(b) and 103(a).

IV. Further Rejections under 35 U.S.C. §103(a)

Other rejections under this section were made as follows:

Claims 7, 9, and 11 were rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*, above, in view of Connolly *et al.* (U.S. Patent No. 6,342,370).

Claim 16 was rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*, above, in view of Gilmanshin *et al.* (U.S. Patent No. 6,263,286).

Claim 17 was rejected under 35 U.S.C. §103(a) as being unpatentable over Summerton *et al.*, above, in view of Gilmanshin *et al.*, above, and further in view of Hearn *et al.* (U.S. Patent No. 4,279,724).

The rejections are respectfully traversed in light of the following remarks.

A. The Invention

The applicant's invention, and the benefits thereof, are discussed above in Section II.

B. The Cited Art

The primary cited reference, U.S. Patent No. 5,034,506, is discussed above. This reference provides no suggestion of the method of independent claim 1 and its advantages over conventional separations of substantially uncharged oligomers. The present invention is based on the discovery that duplexes of the different substantially uncharged analyte molecules with a specific charged probe molecule can be separated from each other on a charge-bearing separation medium.

The secondary references were cited for their disclosure of various individual features of dependent claims 2-27.

Connolly *et al.* is cited for the disclosure of polynucleotides containing deletion variant sequences. The polynucleotides are nucleic acids, such as RNA or DNA (see column 3, lines 29 and 60-62 of the reference). They are clearly not "composed of linked subunits of which at least 90% are uncharged". The polynucleotide can be used as probes for diagnosis of disorders related to mutations in the DNA of an individual (e.g. column 2, lines 46-50). There is no suggestion of forming duplexes of the variant polynucleotides with a charged probe molecule and separating the duplexes.

Gilmanshin *et al.* is cited for the disclosure of fluorescent labeling and the use of electrophoresis. Both of these techniques are, of course, used in many different technologies,

including DNA sequencing. In the sections of this reference pointed out by the Examiner, short labeled probes are used to bind to a DNA which is to be sequenced. The distance between the probes on the DNA is determined, e.g. by FRET (column 10, line 64 and following). The probes can then be removed from the DNA by denaturation, e.g. under electrophoresis (column 19, lines 14-21: "denaturation of the DNA sample...The dissociated probes are removed, e.g. by electrophoresis..."). The reference does not teach or suggest electrophoretic separation of duplexes.

Hearn *et al.* is cited for its disclosure of a superimposed pH gradient, for use in "preparative electrofocusing of protein mixtures" (column 1, lines 47-49). There is no discussion of oligomeric duplexes of any sort.

The teachings of these references, directed to various technologies, provide no guidance regarding a method of separating duplexes comprising different, substantially uncharged oligomeric molecules and a specific charged probe molecule. Even if the teachings of the secondary references were combined with that of Summerton *et al.*, these combined teachings would not suggest the claimed method.

In view of the foregoing, the applicant respectfully requests the Examiner to withdraw the rejections under 35 U.S.C. §103(a).

V. Conclusion

In view of the foregoing, the applicant submits that the claims now pending are now in condition for allowance. A Notice of Allowance is, therefore, respectfully requested.

If in the opinion of the Examiner a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4403.

Respectfully submitted,

Date: 9-3-2003

LeeAnn Gorthey
Registration No. 37,337

Correspondence Address:
PAYOR NUMBER 22918
PHONE: (650) 838-4403
Fax: (650) 838-4350